O-Protonation of Amides in Dilute Acids

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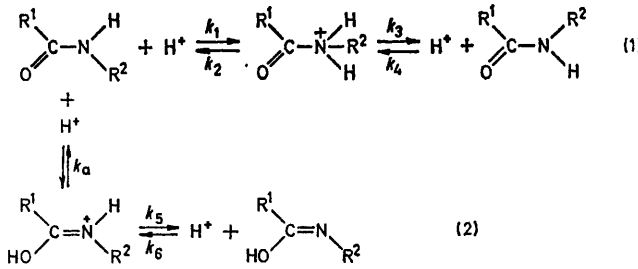
Summary Analysis of proton exchange rates indicates that amides are predominantly *O*-protonated in dilute acids; for *N*-methylacetamide the molar ratio of *O*- to *N*-protonated species is greater than 10^6.

THE question of *O*- *vs.* *N*-protonation of amides in dilute acids has recently been raised anew. Decisive n.m.r. evidence for *O*-protonation in strongly acid media is not considered applicable to less acid solutions. Though granting predominant *O*-protonation in strongly acid solutions when protonation is complete, some authors have claimed that *N*-protonation is dominant in dilute acids and throughout most of the protonation region up to virtually full protonation.[1,2] In formamide both *cis* and *trans* couplings of the C-bound hydrogen with the N-bound hydrogen atoms collapse in the protonation region and it has been asserted that this is consistent only with *N*-protonation.[2] However, since both N-bound hydrogen atoms undergo acid-catalysed exchange at comparable rates, simultaneous collapse is expected, and no conclusion concerning the site of protonation is obtainable from this result.



The molar ratio of *O*- to *N*-protonated amide species in dilute acid solutions can be assessed by consideration of exchange rates measured at acidities where the amide is

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only fractionally protonated. This communication provides quantitative estimates of the ratio from measurements of N-bound hydrogen exchange. Acid-catalysed exchange and *cis–trans*-isomerization of amides have been described by a mechanism involving an *N*-protonated intermediate.[3] Because this accepted mechanism does not appear to account fully for the exchange rate of less basic amides and metal complexes of amides an additional kinetic pathway is suggested.

The accepted mechanism of acid-catalysed exchange and isomerization of amides is *via* an *N*-protonated intermediate.[3] Considering only mechanism (1), and assuming a low steady-state concentration of the *N*-protonated species, the second-order rate constants for exchange and isomerization of an *N*-monosubstituted amide are given by: $k_{ex} = k_1/2$ and $k_{iso} = k_1k_3/(k_2 + k_3)$. For most amides with different substituents on nitrogen the *trans*-isomer is more stable than the *cis*, so that $k_2 > k_3$. When the *cis*- and *trans*-isomers are identical as for *NN*-dimethylacetamide, $k_{iso} = k_1/2$.

For *N*-methylacetamide (NMA) exchange occurs in dilute acid solutions and, at 25°,[3,4] $k_{ex} = 400$ s^{-1} M^{-1} and hence $k_1 = 800$ s^{-1} M^{-1}. Taking $k_2 = 10^{10}$ s^{-1}, for a diffusion controlled deprotonation in the thermodynamically favoured direction,[5] we find the acidity constant $K_{2,1} = k_2/k_1 = 1{\cdot}3 \times 10^7$ M. This value is more than 2×10^6 times greater than the measured acidity constant,[6] $K_a = 5$. Therefore, the *N*-protonated species of mechanism (1) cannot be the common one in dilute acid solutions. Taking the major protonated species as *O*-protonated, we find the molar ratio of *O*- to *N*-protonated amide to be given by $K_{2,1}/K_a$. For NMA this ratio is 3×10^6. This high ratio is evidence for predominance of the *O*-protonated species in dilute acid solutions.

Because of the relative values of the coupling constants involved, only the exchange rate of NMA may be measured by ^{1}H n.m.r. spectroscopy even though isomerization evidently also occurs at low degrees of protonation. *NN*-Dimethylacetamide undergoes isomerization in dilute acid solutions with a rate constant[7] at 25° $k_{iso} = 275$ s^{-1} M^{-1}. The comparable values of k_{ex} and k_{iso} for the two acetamides superficially constitute evidence in favour of mechanism (1), but since the dialkylamide is twice as basic[6] it might be expected that k_{iso} should be greater than k_{ex} for this pair. The greater value for k_{ex} suggests that a more ready pathway for exchange may exist.

As in the acetamide derivatives mentioned above, the methyl couplings in *N*-methylformamide collapse in dilute acid solutions when only a fraction of the molecules are protonated.[2] For *NN*-dimethylformamide, however, the methyl doublet does not coalesce until about 80% protonation.[2] Thus in support of the comparison of acetamides, the rate of exchange of *N*-methylformamide appears to be appreciably greater than the rate of isomerization of *NN*-dimethylformamide.

An alternative exchange mechanism (2) occurs through *O*-protonated amide. Exchange occurs *via* loss of *N*-bound hydrogen in an *O*-protonated intermediate. By this mechanism the first order rate constant for exchange is given by $k = k_5(H^+)/[(H^+) + K_a]$. As exchange is measured by ^{1}H n.m.r. spectroscopy in dilute acid solutions where only a fraction of an amide is protonated, the second-order rate constant for acid-catalysed exchange by mechanism (2) becomes $k'_{ex} = k_5K_a$. In this case the rate of exchange may exceed that of isomerization. Isomerization may proceed only by mechanism (1).

With the observed values given above for NMA, consideration of exchange as occurring *via* *O*-protonated amide yields $k_5 = 2 \times 10^3$ s^{-1}. For the favoured diffusion-controlled protonation in the reverse direction,[5] $k_6 = ca.$ $10^{10.3}$ s^{-1} M^{-1} so that the acidity constant $K_{5,6} = k_5/k_6 = ca.$ 10^{-7}M. This value lies within the range observed for Schiff bases of aliphatic amines.[8] Therefore, for NMA the proposed alternative mechanism (2) for exchange appears competitive with the accepted mechanism (1) and may be dominant for less basic amides. The total exchange rate is given by the sum of that due to mechanisms (1) and (2). Both mechanisms (1) and (2) predict similar collapse of peaks on exchange.

It may be shown that exchange in weakly basic urea proceeds almost exclusively by mechanism (1) but that the *O*-protonated species is still predominant in dilute acid solutions. Two investigations agree that for urea near 25° the second-order rate constant for acid-catalysed exchange,[9] $k_{ex} = 7 \times 10^6$ s^{-1} M^{-1}. With $K_a = 0{\cdot}6$ mechanism (2) gives $k_5 = 4 \times 10^6$ s^{-1}. Again taking the diffusion-controlled limit for k_6 gives $pK_{5,6} = 3{\cdot}7$. Since this value is substantially less than $pK_a = 9{\cdot}7$ for *O*-methylisourea hydrochloride,[10] mechanism (2) is not tenable for exchange in urea. By mechanism (1) $k_1 = 3\,k_{ex}/2$ and with $k_2 = 10^{10}$ s^{-1} one obtains $K_{2,1} = 10^3$M. The molar ratio of *O*-protonated to *N*-protonated urea is given by $K_{2,1}/K_a = 1700$. Thus the faster exchange of urea hydrogen atoms over those of NMA is due partly to its eight times greater basicity, but mainly to its 2000 times greater ratio of *N*- to *O*-protonated amide. Urea provides a clear example of an exchange pathway *via* the *N*-protonated species with predominant *O*-protonation in dilute acid solutions.

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